Fourier analysis. A program has been written to perform a Fourier analysis of electron diffraction data from thin metal films and to resynthesize the original data from its Fourier components for verification of the analysis. The Fourier components and the resynthesized data are displayed on the oscilloscope along with the original data. The analysis and resynthesis carried to 50 harmonics takes about one minute.

Resolving a sum of decaying exponentials. A problem in compartmental analysis required a program to resolve a sum of decaying exponential signals into its individual components. This was done by displaying on the oscilloscope the logarithm of the wave form being analyzed and fitting a straight line to portions of the resulting curve. With the parameter knobs, the experimenter adjusted the slope and position of a straight line also displayed on the oscilloscope to get the best fit to the data. The component thus determined was subtracted from the original wave form and the process repeated with the remainder until all of the components were resolved.

Processing of single-unit data from the nervous system. Programs have been written to determine, from microelectrode recordings, the times at which single neurons fired, and to calculate the distribution of intervals between successive firings. These programs can also be used to determine the distribution of firing times following the presentation of a discrete stimulus.

Cursor program. An experimental curve stored in the memory of the LINC can be displayed on the scope along with an adjustable cursor mark. This cursor designates a desired point on the curve and its locations is controlled by a parameter knob. The amplitude of the point under the cursor is displayed numerically on the scope.

Arterial shock wave measurements. A LINC program has been written to make comparative hydrodynamic measurements in the ventricular cerebrospinal system in order to determine the dissipation and attenuation factors in shock waves attributable to the arterial pulse. The LINC program was designed to work directly with amplified signals from straingauges.

In-phase triggering of stimuli from EEG alpha wave. Simple criteria have been applied to portions of EEG signals to identify and mark the occurrence of rhythmic bursts of alpha activity, and to trigger stimuli which are phase-related to the alpha wave.

PART III. PHYSIOLOGY

THE ROLE OF PERIPHERAL RESISTANCE IN CONTROLLING CARDIAC OUTPUT DURING EXERCISE*

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Cardiac output during exercise is directly related to the level of metabolic activity in the exercising muscles.[1,2] The transition from rest to moderate exercise in untrained subjects results in an increase in cardiac output due primarily to an increase in heart rate.[3,4] However, if heart rate is artificially controlled during exercise at a given treadmill speed, cardiac output is independent of the heart rate setting from heart rates of 70 per minute to 240 per minute in a dog running at three miles per hour (m.p.h.).[5] If the treadmill speed is increased to 4 m.p.h., cardiac output promptly increases. These observations clearly suggest that cardiac output is regulated by a closed-loop mechanism during exercise.

In 1931 Koch[6] proposed that the cardiac output is regulated by means of arterial pressure receptors to whatever level is required to maintain a constant arterial pressure in the face of a changing peripheral resistance. It is the purpose of this paper to present an explicit theory of cardiac output regulation derived from a modification of this concept, and to describe experiments performed to test the key element of this theory.

Theory

In FIGURE 1 a block diagram is shown of a hypothesis developed to explain the closed-loop regulation of cardiac output. Each of the boxes in the diagram indicates the link between the input and output of an element in the complex system and may be represented in mathematical form. A quantitative description of some of these links has already been acomplished,[7] while others are still only known in a qualitative way. The symbol M indicates multiplication of two inputs to produce the output.

The theory states that exercise initiates two trends of events. First, the animal is aroused and this level of arousal determines a reference signal to be compared in the central nervous system (probably in the brain stem) to the incoming action potentials from the baroreceptors. Rushmer[4] and others have demonstrated these phenomena in the form of an increase in heart rate

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occurring in the conditioned animal as the experimenter reaches for the switch to start the treadmill. This arousal phenomenon is more prominent in some dogs than others and the extent of response is quite predictable in a given dog from one day to the next.

The second major phenomenon resulting from the onset of exercise is an increased metabolic activity in the exercising muscles. The local chemical environment in the exercising muscles is determined by the level of aerobic and anaerobic metabolism and by the blood flow. As the increased rate of metabolism changes the chemical environment in the exercising muscles, vasodilatation results which is refractory to efferent sympathetic vasocon-

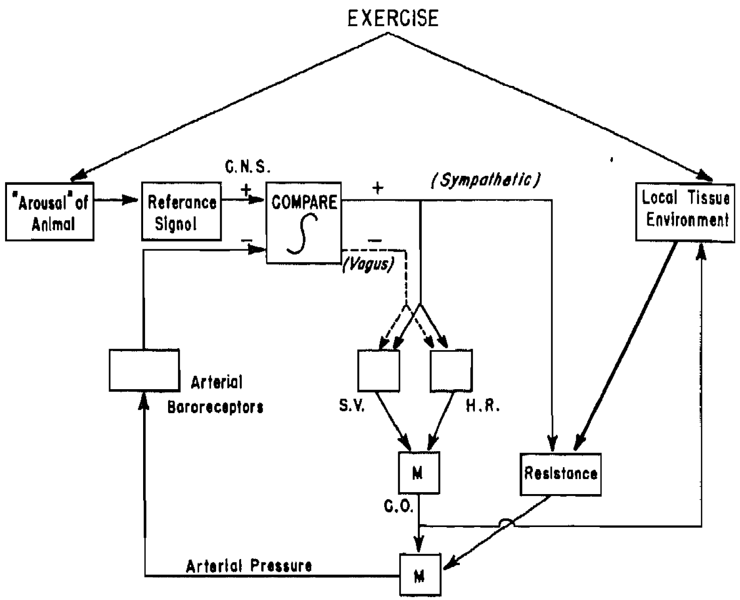


FIGURE 1. Block diagram depicting a theory for control of cardiac output during exercise. This is described in the text.

strictor activity. Since the vascular system is a parallel network, this will result in a fall in total peripheral resistance. By definition, mean pressure is the product of resistance and cardiac output. Thus, a fall is resistance will result in a fall in pressure unless cardiac output has already increased. This fall in pressure is sensed by the pressure receptors, resulting in a decrease in the traffic of action potentials on the afferent nerve from the receptors to the centers of the brain stem. It is postulated that here in the central nervous system (CNS), the signal from the baroreceptors is compared to a reference signal. The sympathetic efferent outflow and the vagus efferent outflow are related to the cumulative difference resulting from this com-

parison, the sympathetic directly and the vagus inversely. Because sympathetic outflow is ineffective in bringing about a sustained reflex vasoconstriction in exercising muscles,[8] the arterial pressure must be restored through an increase in heart rate and/or stroke volume until mean arterial pressure is high enough that the signal from the baroreceptors equals the reference signal in the CNS comparator.

To explain the observed performance of this system, it is suggested that this comparator may act as an integrator, i.e., its output is a function of the cumulative difference between the reference signal and the baroreceptor signal. Thus, a transient positive difference will result in a sustained higher output level of sympathetic activity and lower level of vagal activity. The level of this output will remain constant throughout the exercise run if further differences between the reference and the baroreceptor signal do not develop. If this type of integral control exists, it must be in the CNS component of the system since it has been shown not to exist in the transfer function of the baroreceptor[9] or in the function relating efferent nerve activity to heart rate.[7] The experiments described in this paper were designed to test the key feature of this hypothesis, i.e., the fall in peripheral resistance bears a causal relationship to the rise in cardiac output that occurs during exercise. Not all features of the hypothesis are tested by this study.

Analytical and Experimental Methods

Through a left thoracotomy a 400 cycle per second gated sine wave electromagnetic flowmeter[10] was placed around the ascending aorta of a dog previously trained to run on a treadmill (FIGURE 2). Anesthesia for the operation was accomplished with intravenous nembutal® (30 mg./kg.). A 22-gauge needle with the hub removed was advanced through a carefully machined hole in the keeper of the flowmeter into the aorta with the bevel oriented to record lateral pressure. The proximal end of this needle was connected to a fine polyethylene tube which was brought out through an intercostal space between the scapulae along with the wires from the flowmeter. Each day following the operation the tubing was filled with heparin to prevent clotting. This arrangement permitted continuous measurement of flow and pressure in the dog as he exercised on the treadmill two weeks or more after recovery from this surgery.

In some dogs a second operation was performed two weeks after the first. The left chest was again opened and a 5 cm.-long plastic cylinder was placed around the descending aorta just above the diaphragm. Inside this cylinder was a balloon which, when inflated, compressed the aorta against the cylinder. The tubing connected to the balloon was also brought out through an intercostal space between the scapulae.

Prior to performing any surgery, the dogs were exercised on the treadmill and the time course of heart rate was calculated and plotted by an analog

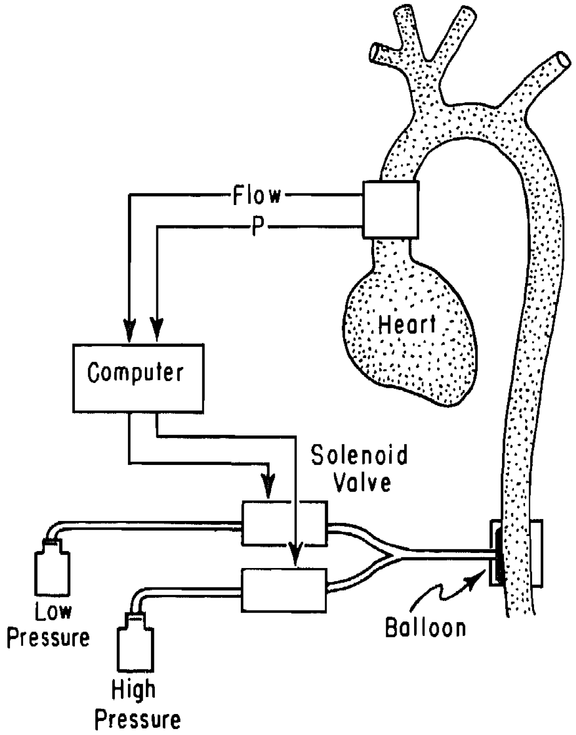
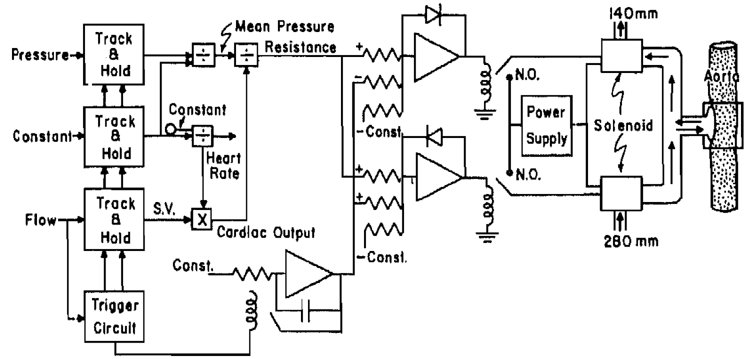


FIGURE 2. Schematic drawing of the experimental arrangement used to record flow and pressure and to control resistance to outflow from the central arterial bed in a dog exercising on a treadmill.

computer from the recorded electrocardiogram.[11] Beginning a week or 10 days after the last operation, the dogs were run each day on the treadmill and the time course of heart rate during treadmill exercise was compared with the pattern observed before surgery. The return of the original heart rate pattern was used as a criterion that the dog had sufficiently recovered from the surgery to justify his being used for the experiments. A strain gauge pressure transducer was strapped to the dog and connected to the polyethylene tube. The electrical signals from the strain gauge and from the electromagnetic flowmeter were fed to the analog computer and beat-by-beat calculations of stroke volume, heart rate, cardiac output, mean arterial pressure, and peripheral resistance over each heart cycle were made. FIGURE 3 illustrates a block diagram of the computer arrangement used to make these calculations and to control air flow into and out of the balloon. The resistance calculated with each heart beat is compared to a reference voltage in the computer. The two comparators are the amplifiers with only a diode in their feedback path. Each comparator is supplied with three signals: (1) the voltage representing peripheral resistance as calculated with each heart cycle; (2) a constant reference voltage; and (3) the output voltage from an integrator whose input is a constant. This integrator, which is triggered to zero with each heart cycle, generates a sawtooth voltage which is fed to one comparator as a positive signal and to the other comparator as a negative signal. If the calculated resistance is greater than the constant, the output of the top integrator is a full 50 volts until the sawtooth voltage representing its third input reaches a value equal to the difference between the calculated resistance and the constant. At this point the output of the comparator falls to zero. Thus, the gain of the integrator determines the duration of each pulse for a given error signal. This 50-volt pulse operates a relay which closes the solenoid valve connecting the balloon to the low-pressure source for a time proportional to the difference between the resistance and the constant. If the resistance falls below the constant, a 50-volt negative pulse appears on the bottom comparator which allows air to enter the balloon. The track and hold circuits are set to trigger just after the end of systole by generating a trigger pulse 60 milliseconds following the point at which flow has decreased from its maximum by an amount equal to one-half the peak resting flow rate. The program for this logic is shown in FIGURE 4.

The concept of resistance as the ratio of pressure to flow is a meaningful index to outflow inpedance from the central arterial bed only when steady state or mean values for flow and pressure are used in the calculation. Otherwise, the capacitance and inertia of the system must be taken into consideration. For this reason, values for flow and pressure must be averaged over a complete heart cycle before using them to calculate resistance. In a



SERVO CONTROL CIRCUIT

FIGURE 3. Analog computer program for measuring mean arterial pressure, heart rate, stroke volume, cardiac output, and peripheral resistance with each heart beat and for controlling total peripheral resistance by affecting resistance to flow down the descending thoracic aorta.

system such as this where the input to the controller is digitized to occur only at the end of each systole and the effect of the change induced in the system by the controller cannot be measured until the next systole, it is important for stable operation that the change in resistance induced by the controller (computer plus balloon system) be completed as quickly as possible. In this system the computer control operation is complete in less than 0.1 second which is considerably faster than the reflex adjustment taking place in the animal. It was found empirically that the most stable performance

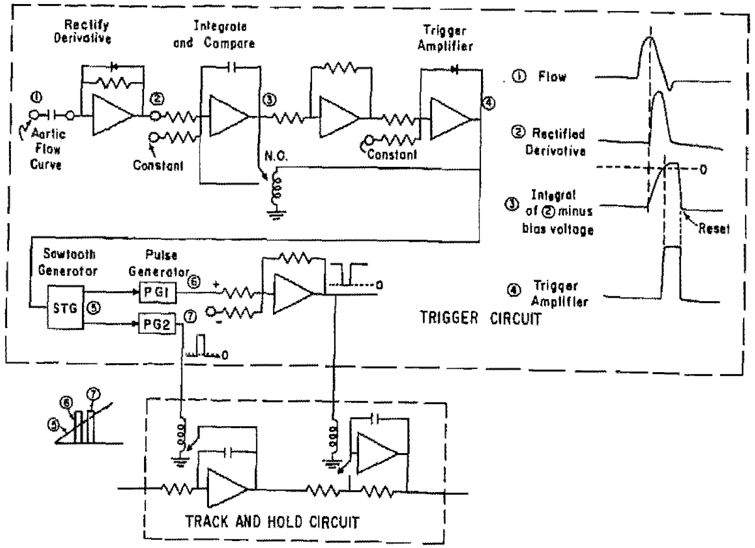


FIGURE 4. Analog computer program for track and hold circuit and logic to trigger initial condition relays at a specified time relative to the aortic flow curve.

occurred when the low-pressure source was maintained at 140 mm. Hg. and the high-pressure source at 280 mm. Hg.

Results

The response of the circulatory system of a dog to treadmill exercise is shown in FIGURE 5. With the onset of exercise, calculated peripheral resistance falls within a few heart beats to less than half its control value. That the fall in resistance preceded the rise in cardiac output is evident from the fact that arterial pressure falls transiently at the onset of exercise. In this dog heart rate and cardiac output more than doubled, while stroke volume changed very little during exercise. Although this response represents the most common pattern observed in our animals, some dogs did exhibit a slight rise in arterial pressure due to an increase in cardiac output that occurred

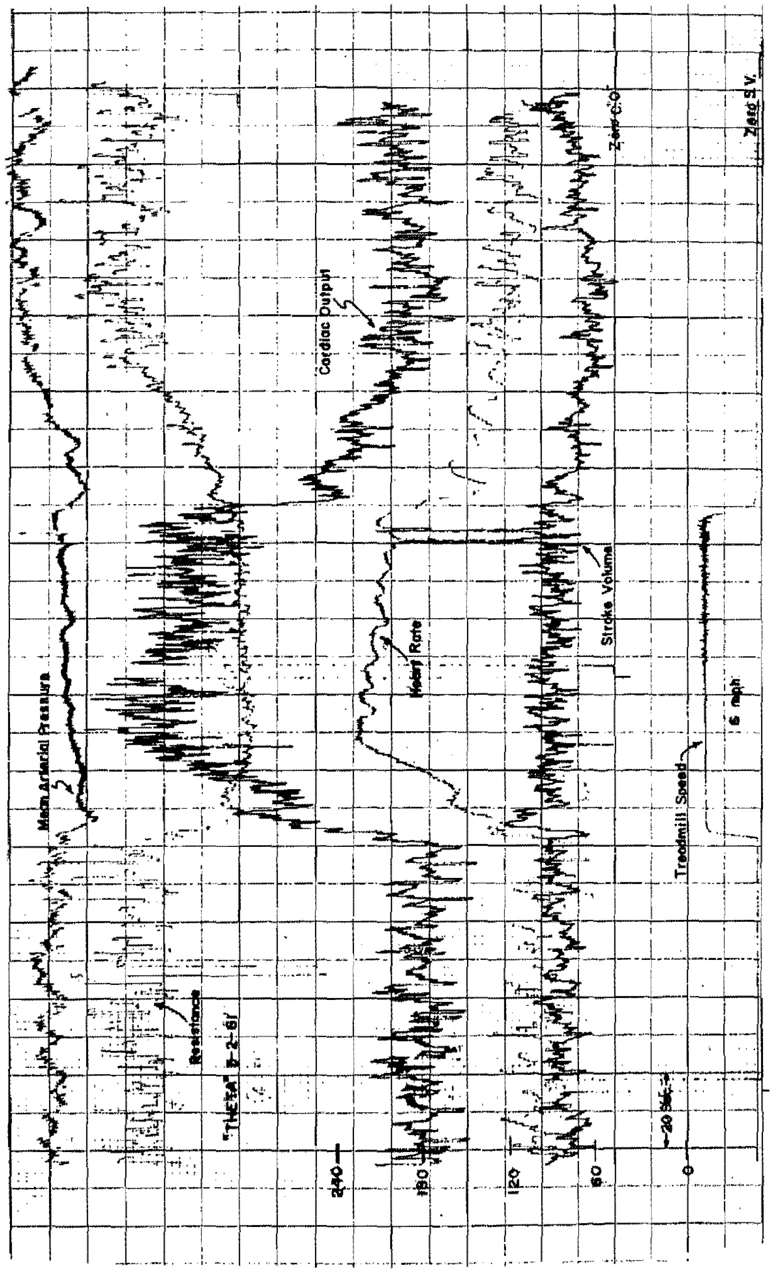


FIGURE 5. Beat-by-beat calculations of mean arterial pressure, peripheral resistance, cardiac output, heart rate, and stroke volume in a dog exercising on a treadmill.

before the treadmill was actually turned on. This is attributed to an arousal of the animal which occurred as the operator prepared for starting the treadmill run.

The response of another dog to treadmill exercise at 4 m.p.h. on a 10 per cent grade is shown in FIGURE 6. Without computer control of resistance,

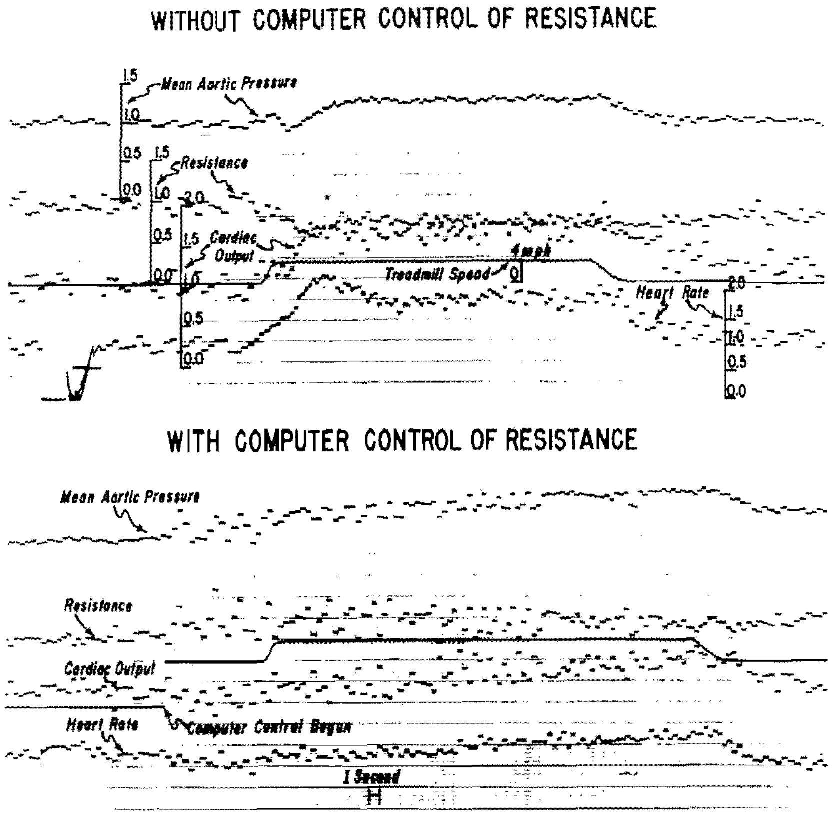


FIGURE 6. *(Top)* Effect of exercise on mean arterial pressure, peripheral resistance, cardiac output, and heart rate when resistance is not controlled by the computer. *(Bottom)* Response three minutes later in the same dog when resistance is controlled by the computer.

heart rate rose 120 per cent above the average resting value within five seconds, while cardiac output at this time exceeded its resting value by 70 per cent. Calculated resistance fell to 56 per cent of its resting value, while arterial pressure fell 13 per cent below and then 14 per cent above the control after eight seconds.

Three minutes after completion of this exercise run, the treadmill was started again at 4 m.p.h. as shown in the bottom half of FIGURE 6. Just

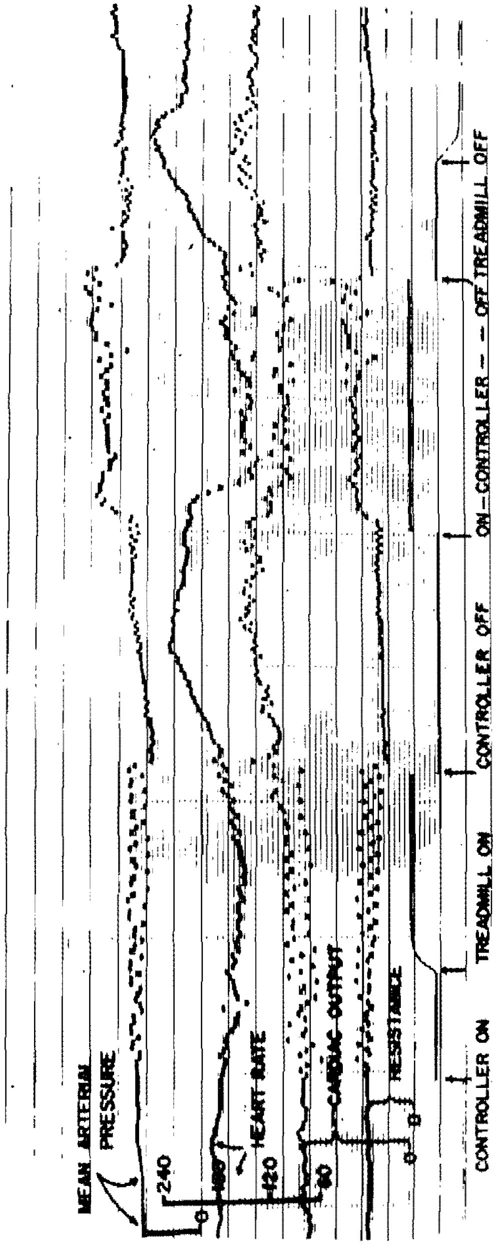


FIGURE 7. Effect of changing the reference level for resistance in the analog computer which controls resistance in the dog. Vertical time lines occur at 10-second intervals.

prior to starting the treadmill, however, the artificial resistance controller described above was activated by introducing a reference voltage slightly higher than the resting resistance to the comparators in the computer. This produced a small increase in measured resistance in the dog and increased the variation in resistance from beat-to-beat. The increased variation in resistance with computer control is due to the fact that the effect of a correction cannot be measured by the system until the end of the next systole. This introduces some instability in this artificial servo loop. When the dog exercised under these conditions, the fall in resistance was prevented by the action of the artificial controller. Heart rate rose only 10 per cent above resting value and cardiac output 12 per cent. The transient fall in mean arterial pressure is not seen, the pressure rising 10 per cent within three seconds after the onset of exercise.

The effect of turning the resistance controller on and off during an exercise run is shown in FIGURE 7. As the controller is turned off, resistance falls immediately below the resting level and remains low, while arterial pressure falls only transiently and then returns to its previous level. This return of pressure is due to an increase in heart rate and cardiac output. When the reference level for resistance in the computer is suddenly increased again (controller on), heart rate and cardiac output fall dramatically but not sufficiently to bring arterial pressure back to its original level. That this may be due to a change in the reference level of the dog's central nervous system comparator (arousal) is supported by the fact that arterial pressure after turning the controller off 20 seconds later, does not fall to the same level as during the previous controller off maneuver.

Discussion

From this study it is apparent that a fall in peripheral resistance plays an important role in bringing about the increased heart rate and cardiac output that occurs in the early phase of exercise. Even though a drop in arterial pressure is not always observed with the onset of exercise, the fall in peripheral resistance does appear to be a *sine qua non* for the production of a sustained increase in heart rate and cardiac output during exercise.

There are other inputs, of course, to the central nervous system than the baroreceptors which are capable of increasing heart rate. In the context of the hypothesis here presented, these inputs, such as excitement and anticipation of starting the treadmill, may alter the reference signal in the CNS comparator but the fundamental determinant of cardiac output during moderate exercise is the state of dilatation or constriction of the blood vessels which in turn is largely dependent during exercise on the metabolic activity of the working muscles.

This model (FIGURE 1) offers an explanation for the observations referred to above on the role of heart rate and stroke volume in determining cardiac

output during exercise. In the normal subject the fractional change in heart rate for a given change in sympathetic and vagal efferent nerve activity (frequency of firing) is five to ten times the fractional change in stroke volume. If heart rate is held constant,[5] however, cardiac output will increase to the same level as before for a given level of exercise by increasing stroke volume, but it will take longer to reach this new level. This is due to the fact that a control system based on an integration of the error signal (reference minus feedback signal) reduces the error to zero regardless of the gain in the loop. Simulation of this model on an analog computer has shown that the model can quantitatively describe the experimental observations.

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